PURE BREAKAGE PBM CALIBRATION IN PHARMACEUTICAL WET GRANULATION

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Framework: wet granulation

Twin-screw granulator:

- **continuous** production of granulated pharmaceutical material for oral solid dosage production
  - pharmaceutical powder mixed with liquid
  - conveyed between co-rotating Archimedes screws alternated with kneading zones

- drying after granulation:
  - formation of solid bonds by crystallisation of solubilised material (binder)

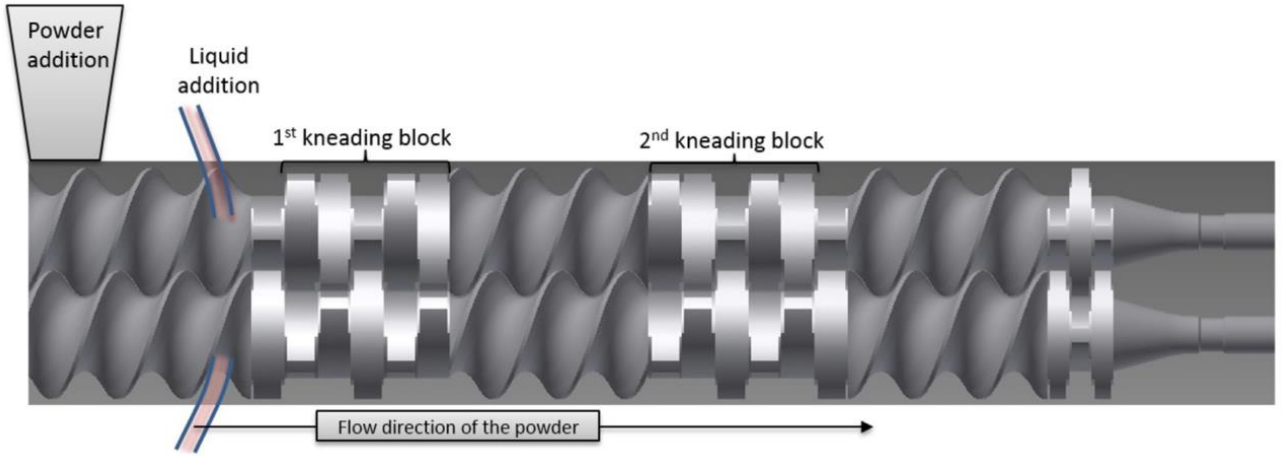

Figure 1. Twin-screw granulator schematic (screw configuration with 12 kneading discs), (*Eur. J. Pharm. Sci.*, 90(2016), 25–37).

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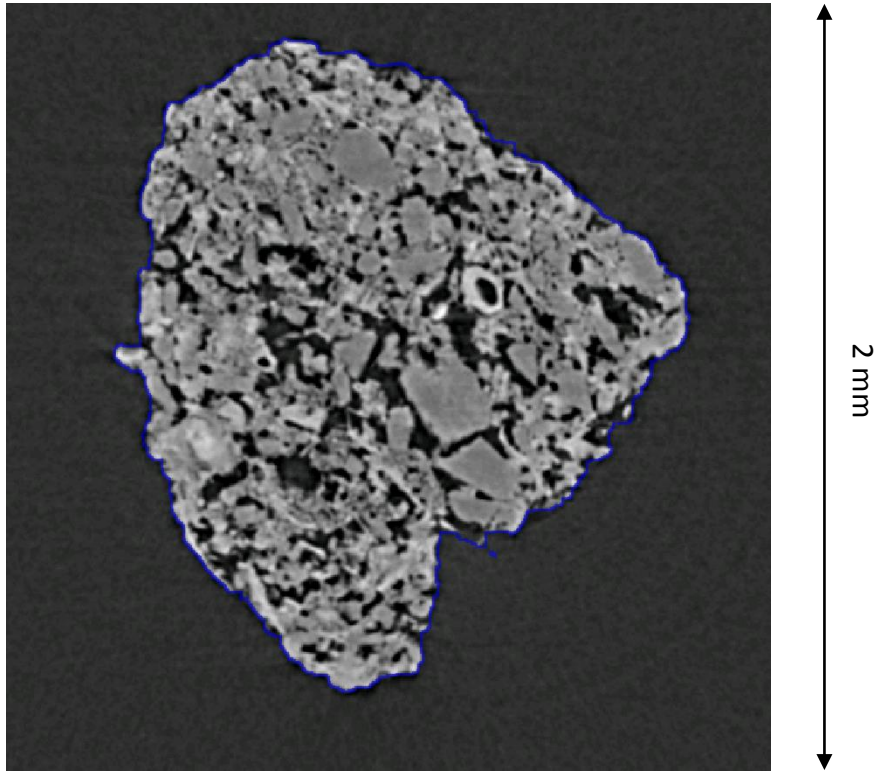
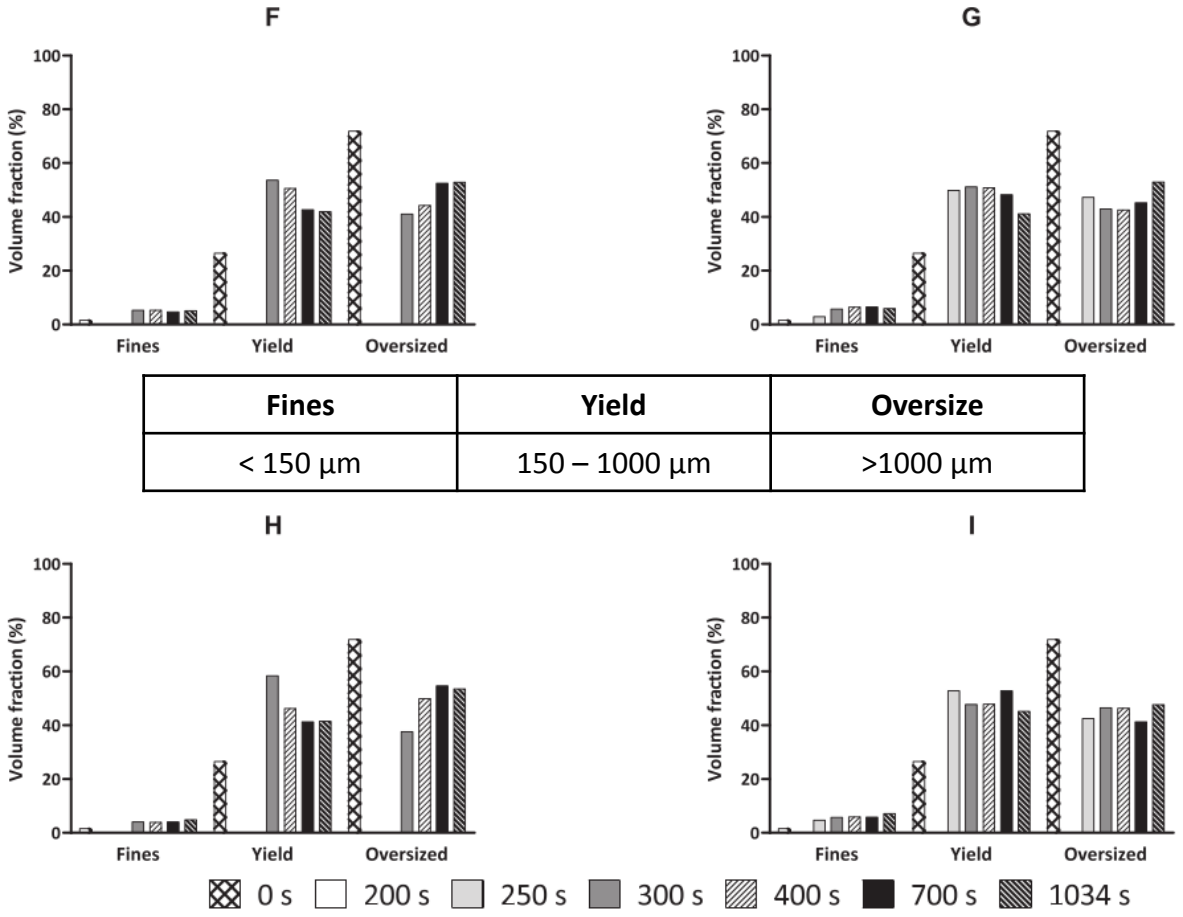


Figure 2. Slice from µCT scan of pharmaceutical granule (obtained at UGCT, Centre for X-ray Tomography)

System: the ConsiGma™ continuous granulation line

Figure 3. ConsiGma™ containing twin-screw granulator, fluid bed dryer, dry transfer line and hopper (GEA Pharma systems).



Fines	Yield	Oversize
< 150 µm	150 – 1000 µm	>1000 µm

Figure 4. Fraction of fines, yield and oversized for experiments F–I (filling time 180s) on the vertical set-up, in function of drying time (*Eur. J. Pharm. Sci.*, 115(2018), 223–232).

System: the ConsiGma™ continuous granulation line

Data collection:

- Dryer variation:
  - drying time, inlet air temperature and flow

- PSD
  - QICPIC™ Dynamic Image analysis system (Sympatec, Clausthal-Zellerfeld, Germany)
  - equipped with a vibrating feeder system (Vibri/L™)
  - Samples of 20g in duplicate

- Moisture content
  - **Loss-on-drying (LOD)** with moisture analyser (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) (infrared dryer and balance, sample of 1g)

Data

“Contradictory” number- and volume-based PSD evolution

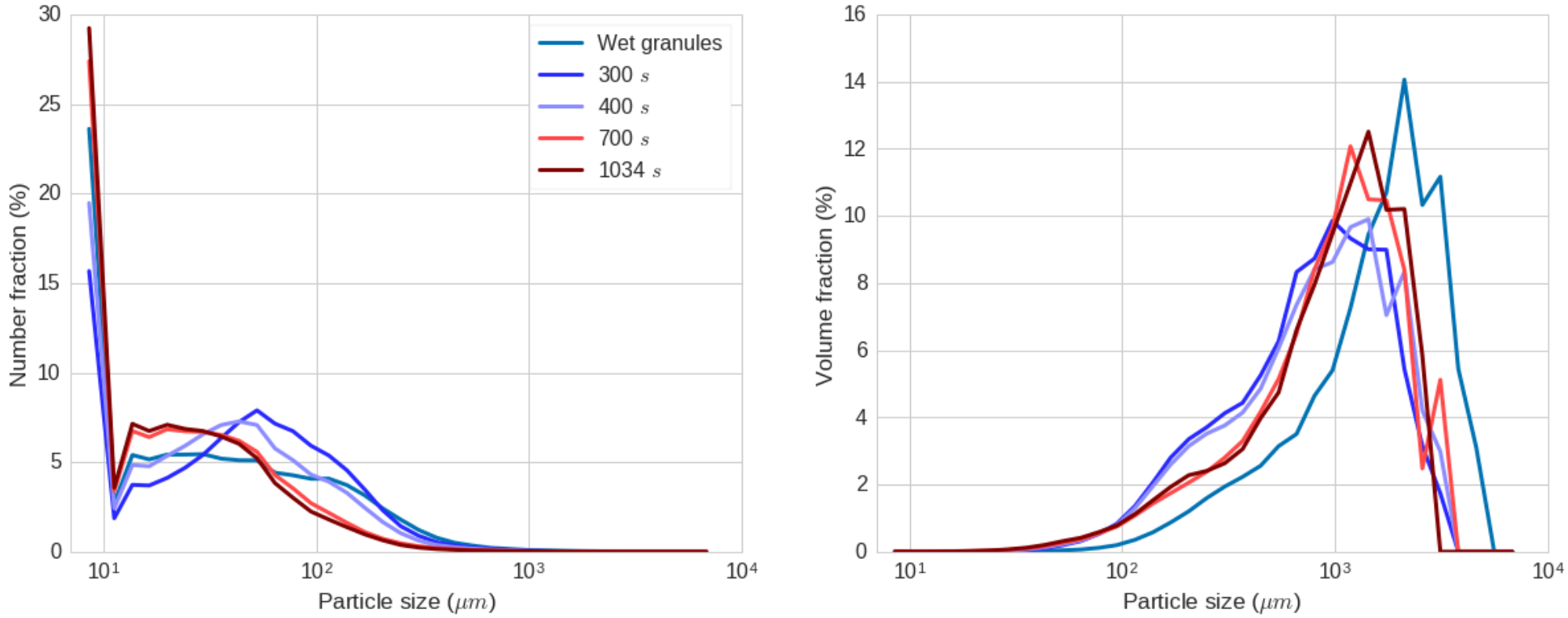


Figure 5. Number- (left) and volume-based PSD of wet granules and granules dried for different time periods, at inlet air temperature of 40°C, inlet air flow of 360m³/h and cell loading of 1kg. PSDs were obtained with QICPIC™ system (Sympatec, Clausthal-Zellerfeld, Germany)

Population balance model

Fragment distributions:

- **Attrition**: lognormal distribution:

$$b_{attr}(\mathrm{x},\mathrm{y},\mathrm{s},\mu) = \frac{1}{\exp(\mu)\mathrm{s}\mathrm{x}\sqrt{2\pi}}\exp\left(-\frac{1}{2}\left(\frac{\log\left({}^{\mathrm{x}}/_{\exp(\mu)}\right)}{\mathrm{s}}\right)^2\right) + \frac{1}{\exp(\mu)\mathrm{s}(\mathbf{y}-\mathbf{x})\sqrt{2\pi}}\exp\left(-\frac{1}{2}\left(\frac{\log\left({}^{(y-x)}/_{\exp(\mu)}\right)}{\mathrm{s}}\right)^2\right)$$

- **Fragmentation**: equisize distribution:

$$b_{frag}(\mathrm{x},\mathrm{y}) = \delta\left(x-\frac{y}{p}\right)p \qquad \text{with : } p = {}^{y(\frac{D}{2})}\Big/_{y(D)}$$

- **Combined** fragment distribution:

$$b = \mathrm{z}\, b_{attr} + (1-z)\, b_{frag}$$

Breakage rate: power law combined with sigmoid **threshold** function:

$$S(x,\alpha,\beta,S_0) = S_0\frac{1}{1+e^{\alpha(x_{thres}-x)}}x^{\beta}$$

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Calibration

Step-wise, for each experiment:

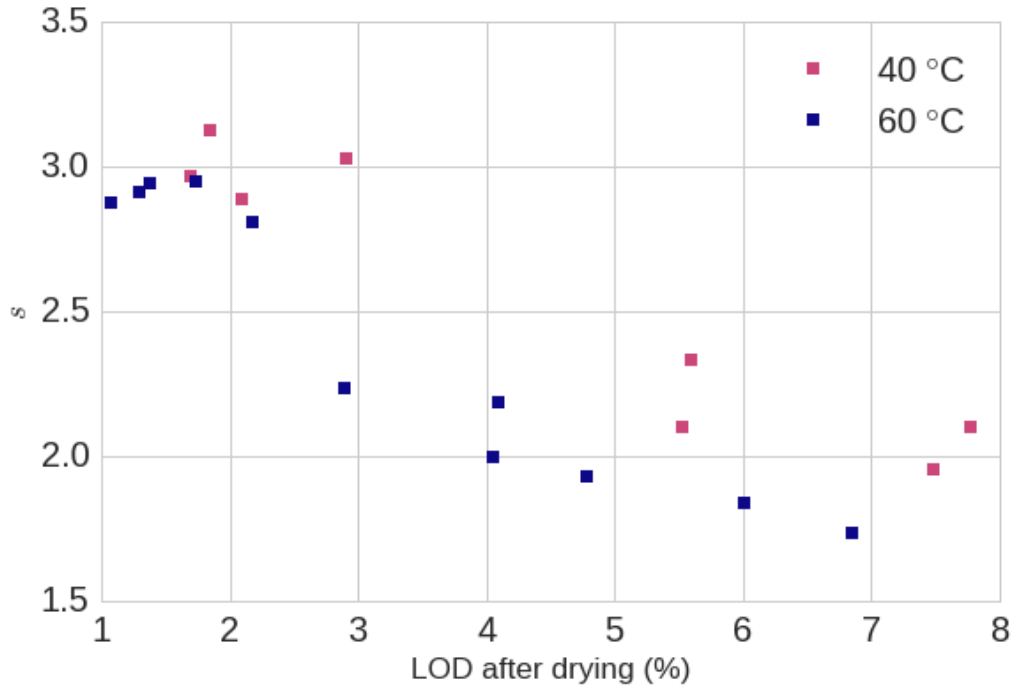
1. Calibration of attrition parameters to number fraction distribution
   - PBM: version with only attrition (*z = 1*)
   - Objective function: SSE between simulation and data in number-based distribution
   - Algorithm: L-BFGS-B (local)

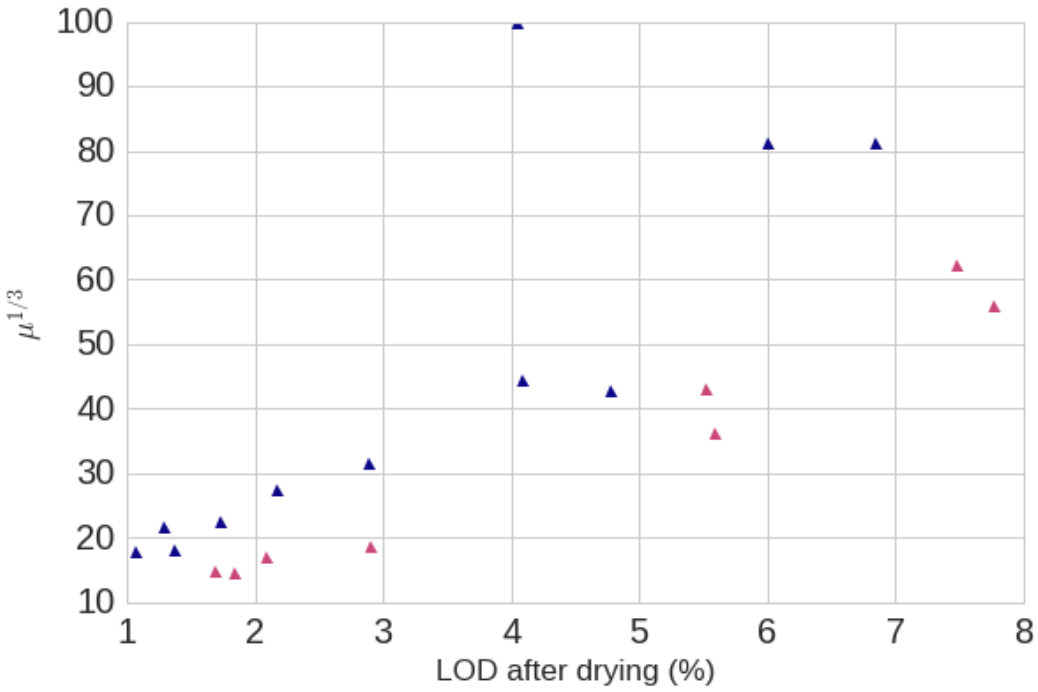
2. Calibration other parameters
   - PBM including attrition and fragmentation
   - Objective function:
     - SSE between simulation and data in volume-based distribution
     - weighted in function of size u: $W(\mathrm{u}) = {}^{1}/_{log10(u)}$
   - Algorithm: brute-force (global)

Results: attrition

Parameters lognormal distribution:

mean diameter and shape correlated with moisture content (LOD), and temperature



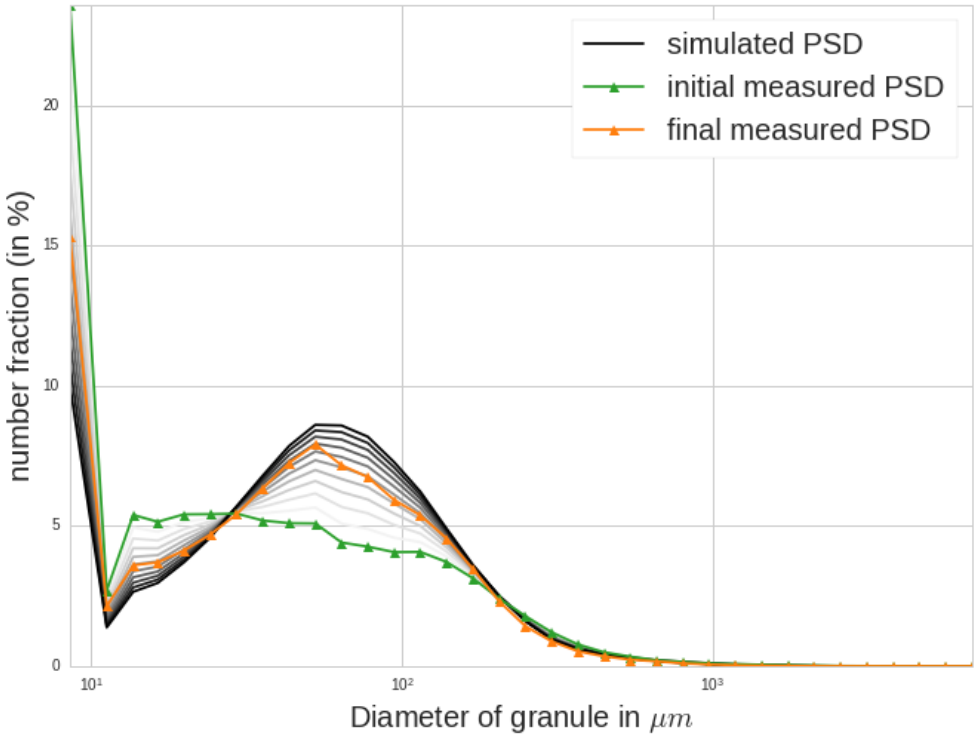


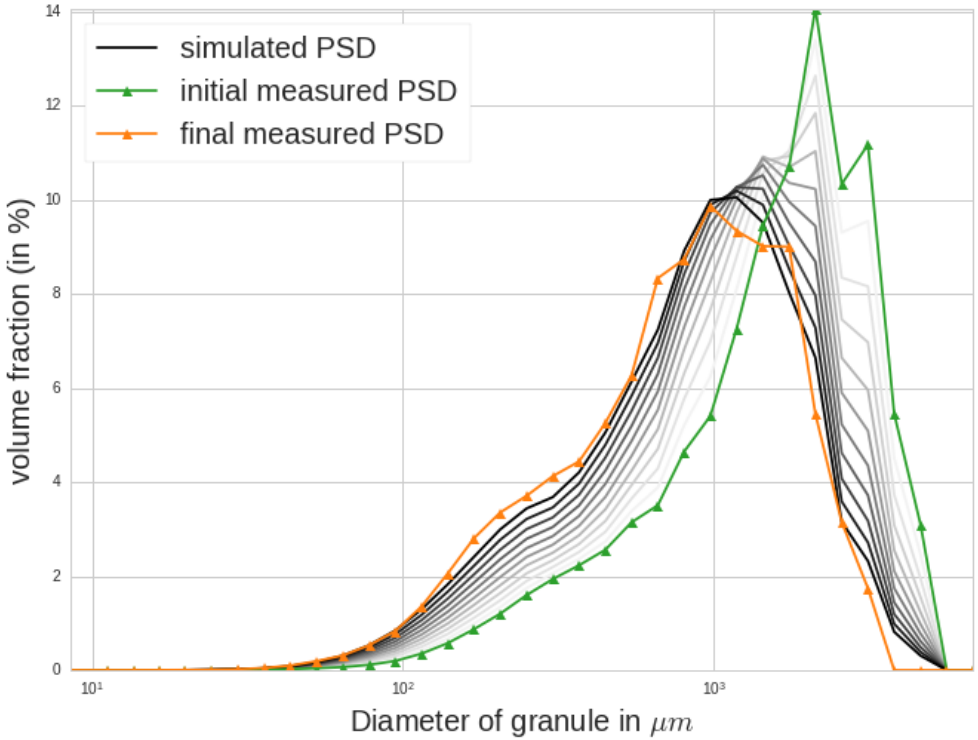
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C

Inlet air flow: 360 m³/h

Drying time: 300 s



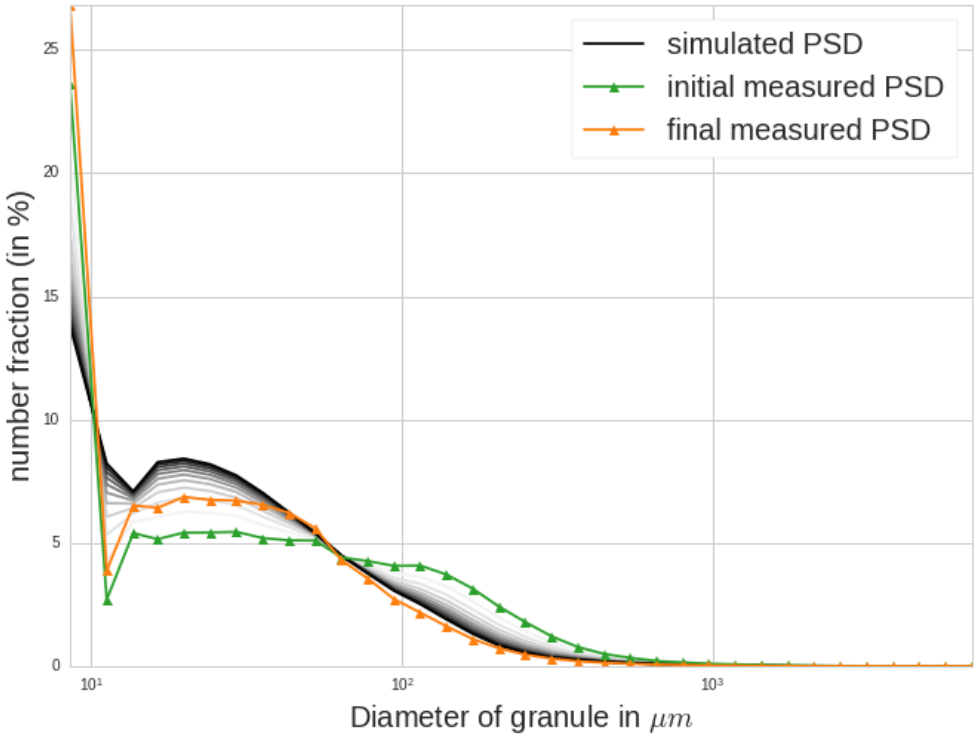


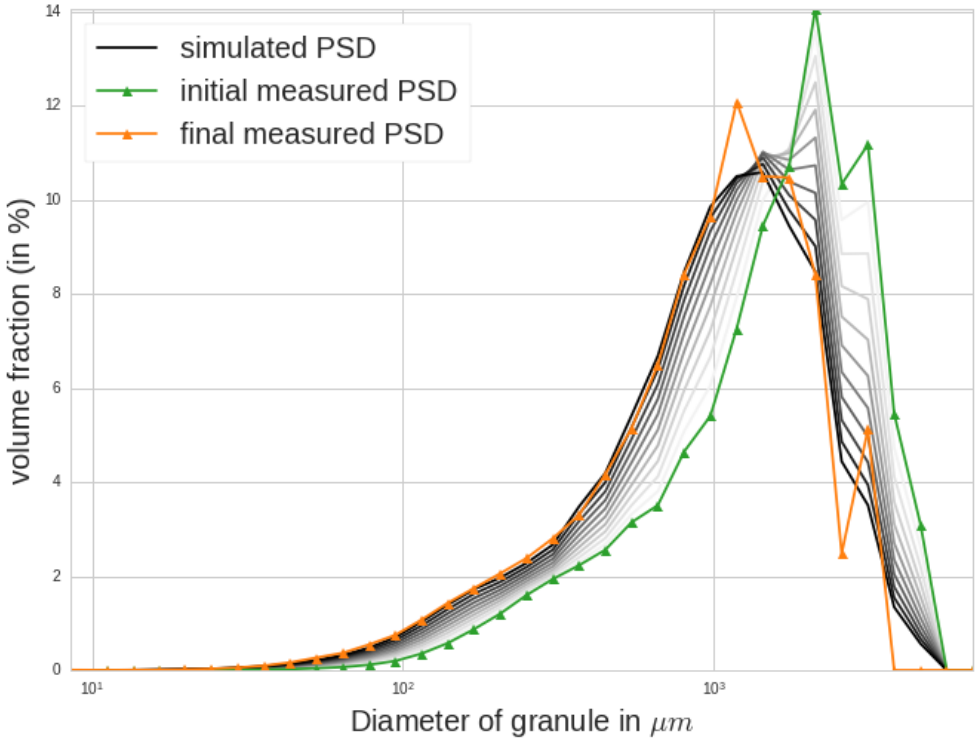
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C

Inlet air flow: 360 m³/h

Drying time: **700** s



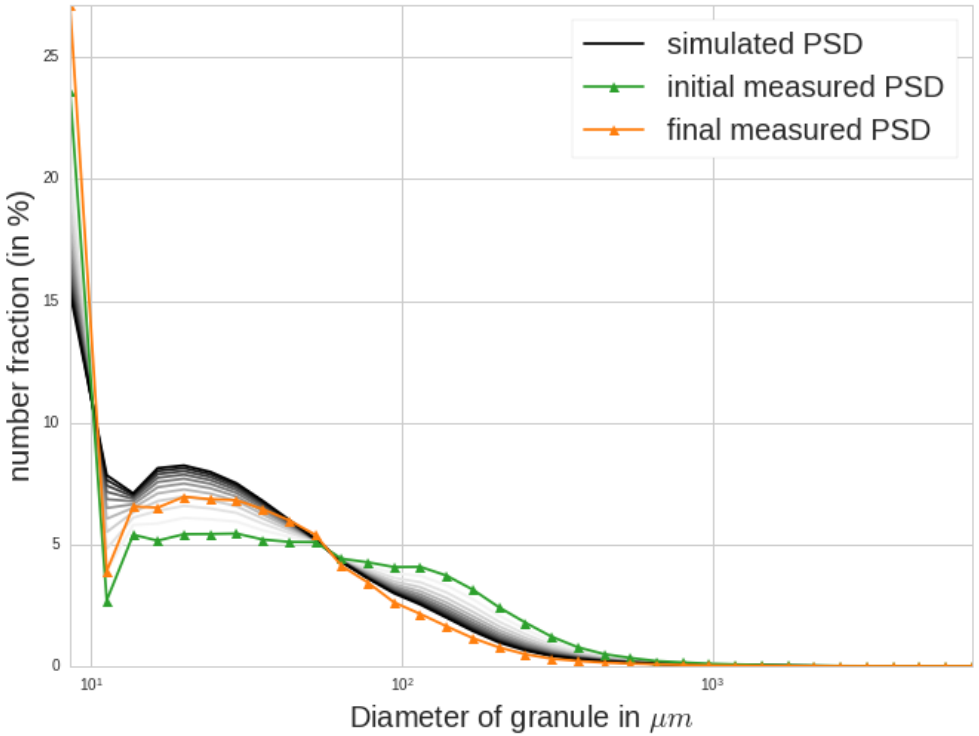


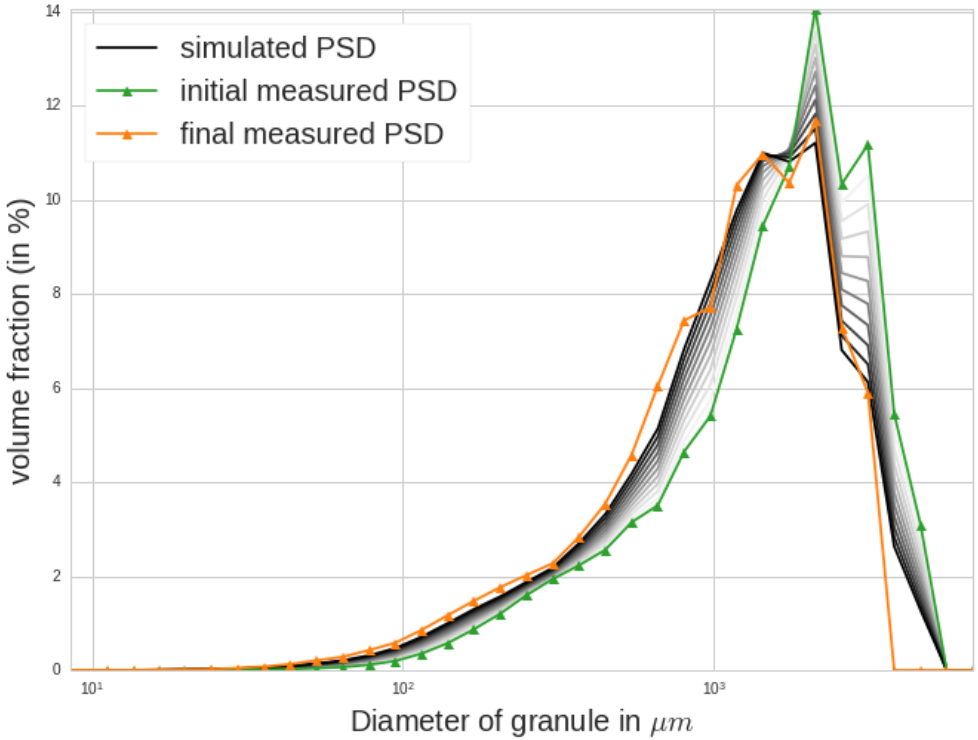
Results: simulated vs experimental PSDs

Inlet air temperature: **60°C**

Inlet air flow: 360 m³/h

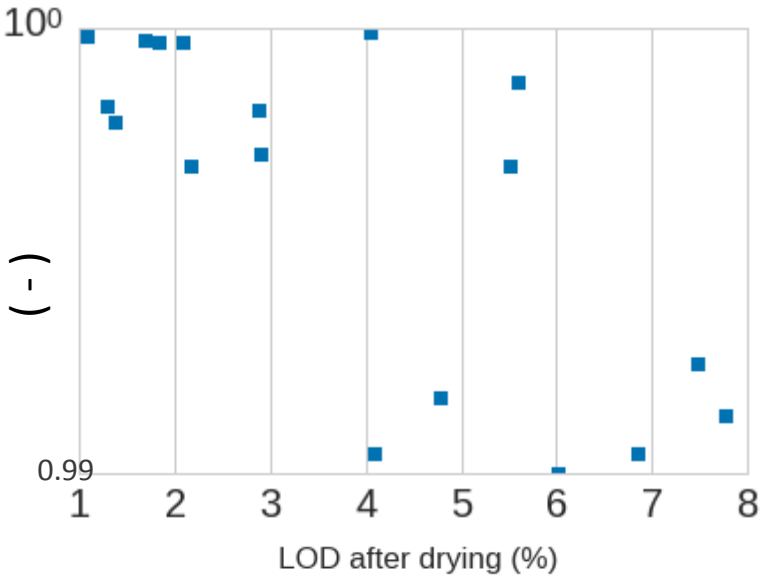
Drying time: 300 s



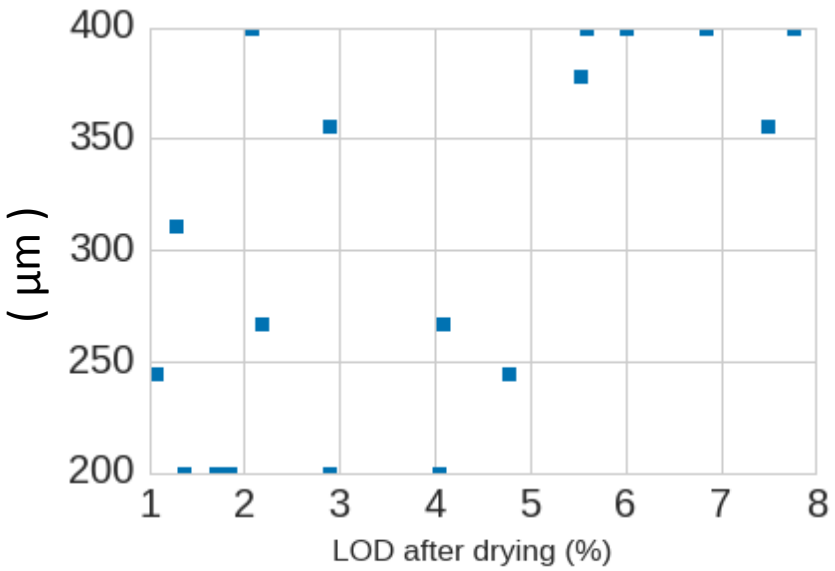


Calibrated parameter values

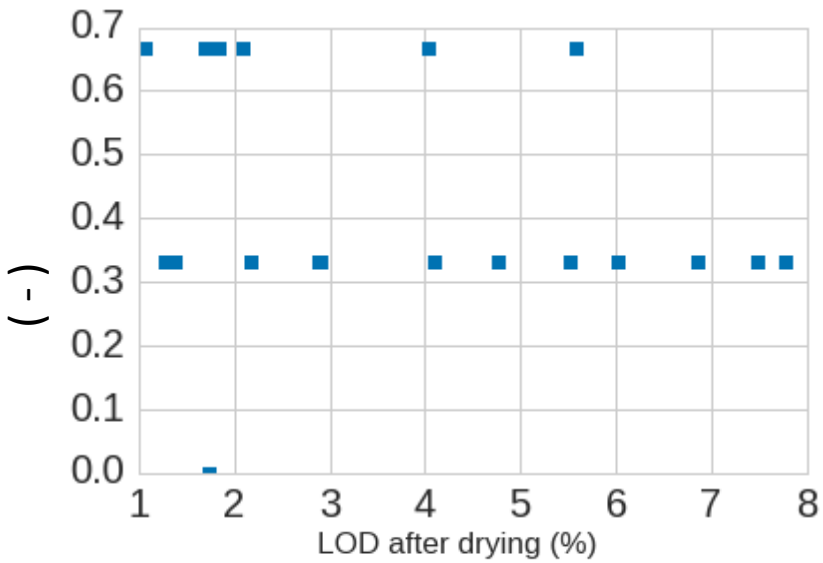
Ratio *z*



Threshold



Power



Conclusion

Study of granule breakage phenomena on different length scales

- needed to capture breakage in detail
- kernels still to be evaluated ➔ parameter identifiability
  - objective function (beware of over-fitting)
  - model validation to be performed
- breakage related to granule moisture content after drying

Thank you for your attention

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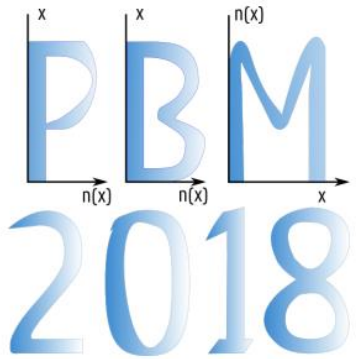

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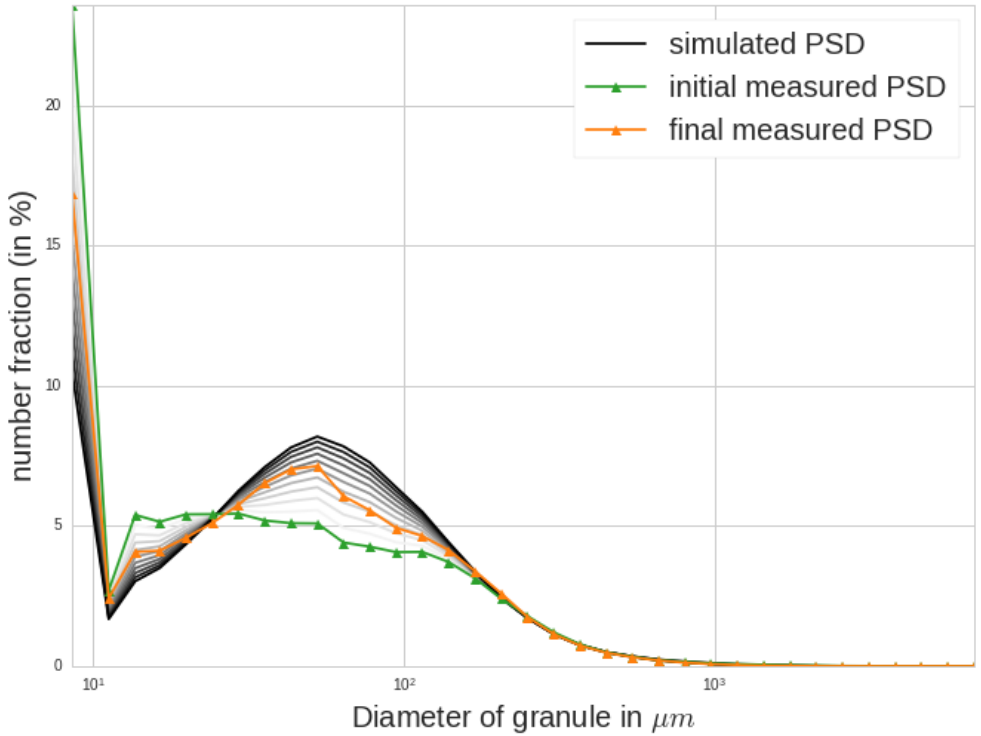
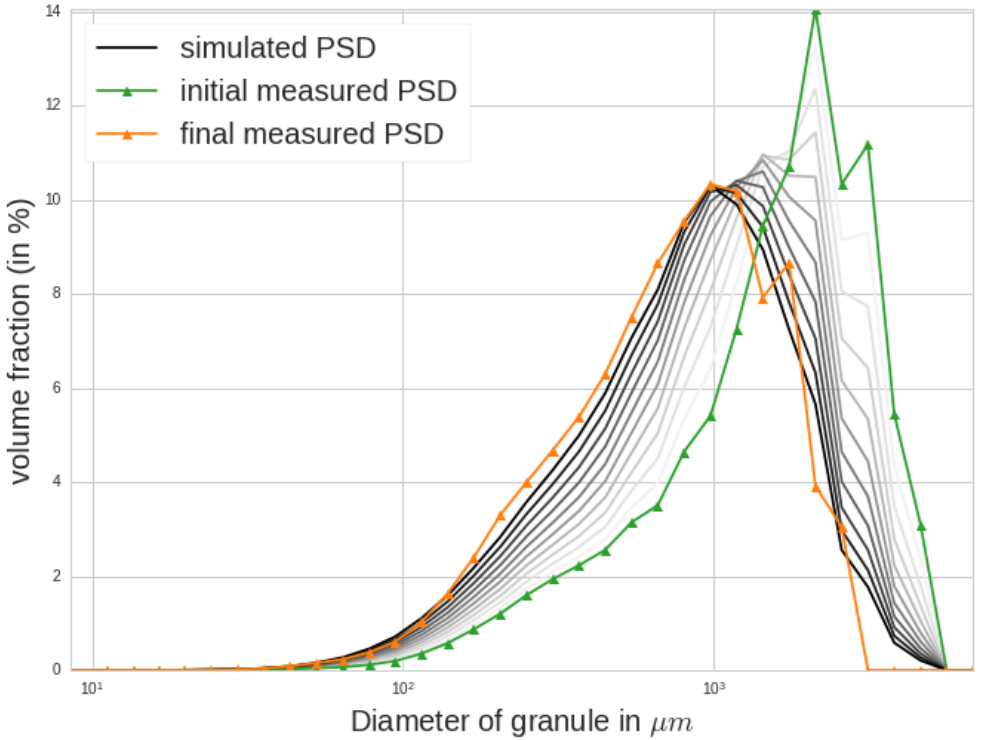
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C

Inlet air flow: **440** m³/h

Drying time: 300 s





Results: simulated vs experimental PSDs

Inlet air temperature: 40°C

Inlet air flow: 360 m³/h

Drying time: **400** s